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Effects of Drugs—Immunosuppression

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In the early 1960s, the "immunologic surveillance" theory of cancer prevention gained wide acceptance (Thomas 1959; Burnet 1970). This theory contended that, in all humans, neoplastic cells were arising repeatedly throughout life but that these clones of cells were rejected and eliminated by the cellular immune system of the host. A logical corollary of this theory was that anything that would impair this cellular immune system would then lead to clinically overt malignancies. Based on this reasoning, it was hypothesized that patients taking immunosuppressive drugs would experience extremely high rates of almost all forms of malignancy. Since 1968 (*Lancet* 1968; Anon. 1972; Penn 1975), accumulated case reports have indicated that the risk of reticulum cell sarcoma is increased in recipients of renal transplants who are receiving immunosuppressive medication. The size and characteristics of the increased risk were difficult to determine because (1) few cases came from any one institution and (2) there was incomplete information on the populations at risk when data from several institutions were pooled. For the same reasons, it was impossible to determine whether the plethora of case reports of other cancers represented a real excess or not.

In 1973, Dr. Fraumeni and I reported on a follow-up study of a large group of renal transplant recipients (Hoover and Fraumeni 1973). We tried to quantify the risks of various types of malignancy and to describe the characteristics of any excess risk observed. This paper will update that report, with over 2½ times more transplant recipients having been studied since the first report. Our resource was the Renal Transplant Registry of the American College of Surgeons. This registry has gone out of existence within the past few months and will be replaced shortly by a registry of patients with end-stage renal disease, which will be maintained by the Department of Health, Education, and Welfare's Bureau of Quality Assurance. Because we have only recently obtained these data, the numbers presented in this paper should be considered preliminary tabulations. I am sure that the overall conclusions will not change between this version and our final report, but we have not as yet

Table 1
Observed and Expected Numbers of Lymphomas and Other Malignancies and Risk Ratios (R.R.) for Men and Women with Renal Transplants

	Men (person-years = 22,351)			*Women (person-years = 14,119)*			*Total (person-years = 36,470)*			
	obs.	*exp.*	*R. R.*	*obs.*	*exp.*	*R. R.*	*obs.*	*exp.*	*R. R.*	*95% C. I.*[a]
All lymphomas	35	2.07	16.9	18	0.79	22.8	53	2.86	18.5	13.9–24.2
Hodgkin's	0	0.95	0.0	1	0.29	3.4	1	1.24	0.8	0.02–4.5
other lymphomas	35	1.12	31.3	17	0.50	34.0	52	1.62	32.0	24.0–42.1
Other cancers	46	23.39	2.0	48	25.65	1.9	94	49.04	1.9	1.5–2.3

Malignancies exclude skin cancers and in situ cancers.
[a] Ninety-five-percent confidence intervals (C. I.) around the risk ratios.

Table 2
Observed and Expected Numbers of Specific Cancers Other Than Lymphomas and Risk Ratios (R.R.) for Men and Women with Renal Transplants

	Men			*Women*			*Total*	
Site	*obs.*	*exp.*	*R. R.*	*obs.*	*exp.*	*R. R.*	*R. R.*	*95% C. I.*
Stomach	2	1.20	1.7	1	0.44	2.3	1.8	0.4–5.3
Colon and rectum	3	3.22	0.9	0	1.94	0.0	0.6	0.1–1.8
Hepatobiliary	5	0.19	26.3	2	0.04	50.0	30.4	12.2–62.6
Lung	7	4.22	1.7	5	0.74	6.8	2.4	1.2–4.2
Breast	—	—	—	9	7.23	1.2	1.2	0.5–2.3
Cervix[a]	—	—	—	7 (2)	1.49	4.7	4.7 (1.3)	1.9–9.7
Bladder	6	1.35	4.4	3	0.30	10.0	5.5	2.5–10.5
Melanoma	4	1.06	3.8	2	0.49	4.1	3.9	1.4–8.5
Brain	1	1.05	1.0	3	0.41	7.3	2.7	0.7–6.9
Thyroid	2	0.43	4.7	2	0.58	3.4	4.0	1.1–10.2
Leukemia	4	1.16	3.4	0	0.34	0.0	2.7	0.7–6.9
Other and unknown[b]	12	9.51	1.3	14	11.65	1.2	1.2	0.8–1.8

[a] In situ cancers of the uterine cervix have been excluded. However, at this time, we have only been able to verify the invasive nature of two of those not reported as in situ. The relative risk in parentheses is the risk that would occur if only these two were actually invasive.
[b] Observed include three soft-tissue sarcomas and two each of the esophagus, pancreas, parotid, and endometrium.

had an opportunity to apply many of the quality control measures that we usually employ. The data concerning the risk of malignancy by various characteristics of recipient and donor will not refer to the entire registry population but to the group in the registry up to a year and a half ago. We should be able to update these tabulations in the near future based on the entire file.

Whenever a transplant was performed at one of the 232 participating hospitals, a report was sent to the Human Renal Transplant Registry (American College of Surgeons) containing identifying and demographic information about the recipient and donor. Follow-up reports on the recipients were made annually by these hospitals. The present study concerns 16,290 patients since 1951 who survived and were followed for at least 1 month after transplantation. The closing date for follow-up was at the end of 1975, but the exact date varied according to institution.

Information on tumors arising in this group was obtained from the routine follow-up inquiries, supplemented in some instances with additional information from published case reports.

Observed numbers of cancers were compared with those expected based on the rates prevailing in the general population. This was accomplished by applying the age-, sex-, and time-specific incidence rates experienced by the general population to the corresponding number of person-years of risk in the study group. The expected numbers of cases were then summed to obtain the total number of cases of various forms of cancer. These values were compared with the observed numbers of cases by means of risk ratios (observed/expected). Ninety-five-percent confidence intervals for these ratios were calculated assuming an underlying Poisson distribution (Haenszel et al. 1962). When the 95% confidence interval does not include 1.0, the ratio is statistically significant at the $p < 0.05$ level.

The incidence rates used to establish the expected values for all sites reported here were from the Connecticut Cancer Registry (1966, 1971). Since 90% of the patients were from the United States, Canada, or Western Europe, these rates probably give a reasonable approximation of the expected numbers of cancers for most sites. Departures from this expectation will be pointed out in the text.

For 11 transplant recipients, there was convincing evidence that a tumor had actually been transplanted from the donor along with the kidney. The donor malignancies included four bronchogenic carcinomas, three renal cell carcinomas, and one each of malignant melanoma, hepatocellular carcinoma, and pyriform sinus carcinoma. These 11 patients have been excluded from the rest of the analyses presented, which concern de novo tumors only.

The risk of lymphoma among transplant recipients is 1.5/1000 patients/year, which is about 19 times that in the general population (Table 1). This excess is present to a similar degree in males and females and is due almost exclusively to a risk of reticulum cell sarcoma, which was approximately 150 times that expected. Fifty percent of these lymphomas were localized to the brain, whereas one would expect less than 1% of lymphomas in general to be so localized. The risk of other cancers was about twice that expected. Much of the site-specific data for other cancers (Table 2) are based on some very small numbers. In addition, several other qualifying points should be kept in

mind when interpreting these data. The excess risk of leukemia is probably attributable to the ionizing irradiation received by two of the three observed cases (one total body irradiation and the other intralymphatic ^{131}I). There is an apparent excess of brain tumors, but, with the marked propensity of lymphomas to be localized to the brain, it may be that these are merely misclassified lymphomas. Malignant melanoma also appears to be in excess, but almost all of the excess can be attributed to an excess of observed cases in the relatively few institutions reporting from Australia. With the marked geographic variation in risk of this tumor, related to sunlight exposure, rates from the Connecticut Registry probably do not summarize adequately the "true" expected experience. Finally, although cancer of the uterine cervix also appears to be in excess, we are not yet confident that all of these are invasive cases (the expected value refers only to invasive cases). In fact, to date, we are only sure that two of them were invasive.

The rest of the site-specific data are remarkable both for those sites that show no excess and for those that do. No excess is seen for a number of the more common tumor types (stomach, colon and rectum, breast). Notable excesses occur for tumors of the liver and gall bladder (the seven cases include four primary liver tumors and three primary bile duct carcinomas), lung, bladder, thyroid, and soft-tissue sarcomas. The lung cancer excess appears to apply only to adenocarcinomas of the lung. The tumors of squamous cell origin, which form the bulk of those in the general population, occur at about their expected frequency. Tumors of the lower urinary tract have been reported in renal transplant recipients and have been attributed to the analgesic abuse that was the cause of the primary renal disease (Wegmann et al. 1974). However, only one of the observed cases in this series could be so attributed. The excess of soft-tissue sarcomas is not so obvious, as the rates from the general population do not allow the segregation of these tumors from the many sites at which they can occur. In this series, there was one leiomyosarcoma of the stomach, one leiomyosarcoma of the small bowel, one synovial sarcoma, and one Kaposi's cell sarcoma of the tonsil. There have been numerous case reports of Kaposi's cell sarcomas of many different sites (Hardy et al. 1976), but only one occurred in this registry's population. Since the thyroid gland is such a radiosensitive organ, a question similar to that for leukemia could be raised for the excess noted here. However, with the information available to us, there is no evidence that any of these observed cases had received an unusual amount of ionizing irradiation.

Table 3 presents the observed and expected numbers of cancers by the interval between transplantation and the diagnosis of the tumor. The onset of the excess risk of lymphoma was explosive, achieving a relative risk of 16-fold within the year following transplantation and remaining at approximately this level throughout the follow-up currently available to us. The excess of other cancers did not appear until 2 years after transplantation, and then it progressively increased with increasing duration of follow-up. We have been able to characterize the excess risks according to various characteristics of recipient and donor (Tables 4 and 5). As mentioned, the numbers in these two tables are less than in the preceding ones, since these tables are based on an earlier analysis of the data from this registry. With the numbers involved, there is little evidence of any difference in risk of lymphoma by type of renal

Table 3
Observed and Expected Numbers of Malignancies and Risk Ratios According to the Interval from First Transplant to Tumor Diagnosis

	Interval (yr)				
	<1	*1*	*2*	*3–4*	*5+*
Lymphoma					
observed	18	14	9	6	6
expected	1.01	0.66	0.46	0.47	0.25
risk ratio	17.8	21.2	19.6	12.8	24.0
Other cancers					
observed	19	13	16	23	24
expected	17.73	11.35	7.73	8.05	4.19
risk ratio	1.1	1.1	2.1	2.9	5.7

disease, number of transplants, or year of first transplantation. There is some evidence of particularly excessive lymphoma risk among those transplanted at a very young age. Similarly, the risk of other cancers does not appear to vary by type of renal disease or number of transplants but seems particularly excessive among those under age 20 at transplantation. The trend seen in risk

Table 4
Observed and Expected Numbers of Malignancies following Renal Transplantation and Risk Ratios (R.R.) According to Characteristics of the Recipient

	All lymphomas			*Other cancers*		
	obs.	*exp.*	*R. R.*	*obs.*	*exp.*	*R. R.*
Recipient's renal disease						
glomerulonephritis	19	0.784	24.2	23	9.664	2.4
pyelonephritis	2	0.175	11.4	3	3.224	0.9
polycystic kidneys	5	0.078	64.1	3	1.661	1.8
other and unspecified	7	0.278	25.2	8	4.101	2.0
Number of transplants						
1	29	1.122	25.8	31	16.188	1.9
≥2	4	0.194	20.6	6	2.461	2.4
Year of first transplant						
before 1965	3	0.128	23.4	7	1.562	4.5
1965–1969	20	0.773	25.9	21	10.485	2.0
after 1969	10	0.414	24.2	9	6.595	1.4
Age at first transplant						
<20	7	0.161	43.5	6	0.649	9.2
20–29	7	0.342	20.5	5	2.043	2.4
30–39	7	0.314	22.3	9	4.710	1.9
40–49	9	0.366	24.6	14	7.287	1.9
50+	3	0.135	22.2	3	3.958	0.8

Table 5
Observed and Expected Numbers of Malignancies and Risk Ratios (R.R.) According to Characteristics of the Donor for Renal Transplant Recipients Receiving One Transplant Only

	All lymphomas			*Other cancers*		
	obs.	*exp.*	*R. R.*	*obs.*	*exp.*	*R. R.*
Relationship of donor						
mono. twin	0	0.034	—	2	0.486	4.1
sibling	4	0.244	16.4	9	3.430	2.6
parent	7	0.185	37.8	3	1.258	2.4
cadaver	17	0.602	28.2	17	10.112	1.7
other	1	0.049	20.4	0	0.790	—
Sex of donor						
same sex	16	0.599	26.7	15	7.812	1.9
different sex	9	0.393	22.9	10	5.813	1.7
donor sex unknown	4	0.122	32.8	6	2.451	2.4
Age of donor						
≤29	7	0.343	20.4	6	4.809	1.2
30–49	9	0.390	23.1	15	5.255	2.9
≥50	4	0.142	28.2	1	2.013	0.5
unknown	9	0.228	39.5	9	3.888	2.3

of other cancers by year of transplantation can be explained on the basis of the trend in risk by interval from first transplantation described above. There is little evidence of a difference in risk of either lymphoma or other cancers by sex of the donor, age of the donor, or the relationship of the donor to the recipient.

In summary:

1. The risk of reticulum cell sarcoma in renal transplant recipients is approximately 150 times that expected based on the experience of the general population.
2. The risk of lymphoma has two very unusual characteristics: (1) it occurs with an explosive onset, achieving a high level of relative risk within the year following transplantation, and (2) it has an extremely high predilection for brain involvement.
3. There is no evidence of any appreciable variation in risk by the type of renal disease of the recipient, the relationship of the recipient to the donor, or single versus multiple transplants.
4. There is a possibility that the *relative* risk of lymphoma is greater among children than among adults.
5. Cancers other than lymphoma occur at approximately twice the expected rate.
6. The excess of other cancers does not appear until 2 years following transplantation and becomes progressively larger with increasing follow-up.
7. The excess of other tumors appears to be attributable to excesses of soft-tissue sarcomas, adenocarcinomas of the lung, primary tumors of the

liver and bile ducts, cancers of the lower urinary tract, thyroid cancers, and perhaps cancers of the uterine cervix.
8. No excesses were noted for many sites, including a number of the more common ones (stomach, colon and rectum, breast).
9. There is little evidence of any appreciable variation in risk of other cancers by a number of characteristics of recipient and donor, with the possible exception of a greater *relative* risk among those receiving transplants prior to age 20.

The logical question at this point is: What does all of this mean? I believe these data have both a pragmatic meaning with respect to renal transplantation and a larger meaning with respect to giving us some insights into possible biologic mechanisms involved in carcinogenesis. As far as renal transplantation is concerned, it is the opinion both of patients with end-stage renal disease and of their physicians that the excess risk of lymphoma (1.5/1000 patients/yr) is an acceptable risk to take in an attempt to achieve the improvement in quality of life brought by renal transplantation.

There are several implications of these data with respect to our understanding of some basic biologic mechanisms of carcinogenesis. These can be summarized in a short review of the hypotheses that have been proffered over the course of the last 15 years to explain the anticipated or observed cancer excesses in these patients. The most prominent of these hypotheses are given in Table 6. The blank space beside 9 is not an oversight. Every time I discuss these data, someone suggests a hypothesis which sounds as creditable as any of the others on this list, so I have left this space to accommodate an addition.

One of the first hypotheses offered was that all of the excess could be attributed to the fact that most of the patients receiving renal transplants were victims of chronic glomerulonephritis. The argument was that chronic glomerulonephritis was an autoimmune disease, that cancer was known to be excessive in patients with autoimmune disease, and that the excesses in the transplant population therefore had nothing to do with transplantation per se. There are a number of flaws in this reasoning, but, aside from this, the emerging data indicate that there is essentially no difference in the excess cancer risk according to the recipient's renal disease.

Table 6
Some Hypotheses Offered To Explain the Excess of Malignancy in Renal Transplant Recipients

Hypotheses
1. Glomerulonephritis
2. Chronic uremia (immunosuppressive)
3. Immunologic surveillance
4. Chemical carcinogenicity of immunosuppressive drugs
5. Oncogenic viruses
6. Chronic antigenic stimulation
7. Graft-vs.-host reaction
8. Combinations of hypotheses 5 and 6 or 7
9.

Chronic uremia, itself a physiologic state associated with immunosuppression, has also been offered as the reason for a cancer excess in the transplant population. There has as yet been no large-scale study of patients with end-stage renal disease who have not received transplants (renal dialysis patients). However, there is a remarkable lack of any case reports of reticulum cell sarcoma arising in patients on dialysis. Given the interest in this question and the observations in transplant recipients, the lack of such case reports in the literature is probably significant. Recently a study was reported which purported to show an excess risk of malignancy in patients with chronic uremia (Matas et al. 1975b). However, the numbers were quite small, and the temporal relationship between the onset of the uremia and the occurrence of the tumors was not well defined. In any case, the observed excesses showed quite a different pattern than those seen for transplant recipients (no excess risk of lymphoma or the other sites noted in this presentation).

I referred to the theory of immunologic surveillance at the beginning of this paper. I think the data clearly show that, in its simplest form, this theory cannot explain what we have observed. There is no across-the-board excess of all tumors. In fact, the tumors that are excessive tend to be those that are quite rare in the general population. Perhaps excesses of the more common tumors will appear as we follow a larger group of patients for longer periods of time. However, if such excesses do appear, the explanation for them will certainly have to be different than the possible explanations for the excesses already seen.

It is possible that the immunosuppressive drugs themselves are carcinogenic. If this is so, it is unlikely to be the explanation for the excess risk of lymphoma. The explosive onset of the excess risk of this tumor is certainly inconsistent with almost any theory of chemical carcinogenesis.

The last four hypotheses listed are the ones that I believe have the most creditability for explaining what we have observed among transplant recipients. Laboratory evidence is quite convincing that the immunosuppressive drugs facilitate infections with oncogenic viruses (Lopez et al. 1974). In addition, it is relatively easy to obtain oncogenic viruses from serum and urine specimens of renal transplant recipients (Matas et al. 1975a). The cancers for which we have noted excesses (reticulum cell sarcoma, soft-tissue sarcomas, hepatomas, and possibly cancers of the uterine cervix) are ones that have been suggested as particularly likely to be due to oncogenic viruses (Allen and Cole 1972; Winters and Morton 1975; Blumberg et al. 1975).

Chronic antigenic stimulation and graft-versus-host reactions, although referring to distinctly different mechanisms, can be considered together. These hypotheses imply that the excess risk of cancer requires both immunosuppression and an underlying, smoldering, lymphoreticular war between the host and the foreign kidney. These phenomena may be responsible for the occurrence of tumors by themselves or in conjunction with activating oncogenic viruses. A large amount of support for these hypotheses comes from relevant laboratory animal experimentation (Schwartz and Beldotti 1965; Schwartz 1975). In addition, other human evidence also tends to support these ideas. Victims of a number of cogenital and acquired disorders are similar to transplant recipients in giving simultaneous evidence of immunodeficiency and immunostimulation with lymphoid hyperactivity. These conditions (primary

immunodeficiency syndromes, nontropical sprue, Sjogren's syndrome, and sarcoidosis) all demonstrate the marked and almost exclusive excess of lymphoreticular malignancies that we see in transplant recipients (Fraumeni and Hoover 1977). Points against these two hypotheses are the lack of any evidence of excessive lymphoma risk among multiple-transplant recipients versus those having just one transplant and a similar lack of excessive lymphoma risk among patients receiving cadaver kidneys versus those receiving them from first-degree relatives. Antigenic stimulation and the likelihood of graft-versus-host reactions should be greatest among recipients of multiple transplants and among less closely "matched" patients. It will be important to establish whether immunosuppression itself can prompt excess malignancies or whether a concomitant immunostimulation is a necessary component. The excess risk of lymphoma among transplant recipients is considered acceptable in the face of the benefits of transplantation. However, the immunosuppressive drugs are beginning to be used for a number of other conditions, many not involving concomitant immunostimulation (Penn 1974). A similar excess risk of malignancy may not lead to a similar risk-benefit decision for these conditions. Although there are case reports of malignancies in these kinds of patients treated with immunosuppressive drugs (Penn 1974), no study has yet appeared to indicate that there is any real excess over that expected. Adequate follow-up studies of these types of patients should have a high priority, since the results coming from them will contribute greatly to our knowledge of the effects of immunosuppressive drugs.

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